PDC N: 8895000000044

CHEMICAL MANUFACTURERS ASSOCIATION

8EHQ-1194-13254

November 7, 1995

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, SW
Washington, D.C. 20460 - 0001

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RE: TSCA Section 8(e): Documents 8EHQ - 1194 - 13254 (1-Hexene: CASRN 592341 6) and 8EHQ - 1194 - 13255 (1-Tetradecene: CASRN 1120361)

Dear Sir/Madam:

In compliance with your request dated January 12, 1995, the Chemical Manufacturers Association (CMA) Alpha Olefins Panel hereby submits one copy each of the following final study reports entitled:

- Reproduction/Developmental Toxicity Screening Test in Rats with 1-Hexene; and,
- Combined Repeated Dose Toxicity Study/Reproduction/Developmental Toxicity Screening Test in Rats with 1-Tetradecene.

The studies were performed at Springborn Laboratories.

This submission is made on behalf of the test sponsors, which are manufacturers of alpha olefins: Albemarle Corporation, Chevron Chemical Company and Shell Chemical Company. Users of alpha olefins represented on the Panel, as test sponsors, are Phillips Petroleum Company and Neste, Finland.

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If you have any questions regarding this submission, please do not hesitate to contact me at 202/887-1305.

Sincerely,

Cecilia W. Spearing

Cecilia W. Spearing
Manager
Isopropanol Panel

cc: CHEMSTAR Alpha Olefins Panel/TRTG

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8EHQ-13, 254

REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

FINAL REPORT

Study Director

Elaine M. Daniel, Ph.D., DABT

Study Completed on

March 24, 1995

Performing Laboratory

Springborn Laboratories, Inc. (SLS)
Life Sciences Division
640 North Elizabeth Street
Spencerville, OH 45887

SLS Study No.

3325.1

Submitted to:

Chemical Manufacturers Association
2501 M Street, N.W.
Washington, DC 20037

Springborn

COMPLIANCE STATEMENT

This study was conducted in compliance with the Environmental Protection Agency Good Laboratory Practice regulations (40 CFR Part 792) and OECD Annex 2 C(81)30.

Elaine M Daniel Date 3/24/95

Elaine M. Daniel, Ph.D., DABT
Study Director
Springborn Laboratories, Inc.

QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the study director in accordance with SLS's Standard Operating Procedures as follows:

Phase	Date
Test Article Receipt	12/03/93, 01/11/94
Reserve Sample	01/21/94
Test Article Formulation	01/24/94
Stability and Homogeneity Sampling/Analysis	02/03/94
Animal Receipt	03/03/94, 03/17/94
Dose Preparation	03/11/94
Randomization	03/14/94
Dosing	03/17/94
Concentration Analysis	03/25/94
Cohabitation	04/11/94
Plug/Vaginal Smear	04/12/94
Necropsy	04/26/94, 05/11/94
Organ Weights	04/26/94
Body Weights	04/28/94, 05/11/94
Food Consumption	04/28/94
Clinical Observations	04/29/94
Parturition	05/10/94
Pup Viability/External Examination/Sex Determinations	05/11/94
Processing, Staining, Tissue/Slide/Block Accountability and Histology Worksheets	06/23/94, 07/07/94, 07/11/94
Tissue/Slide/Block Accountability and Histology Worksheets (for additional Kidneys)	08/26/94
Data Audits	07/08/94, 07/14/94, 07/15/94, 07/18/94
Draft Report Review	09/20/94
Final Report Review	03/24/95

QUALITY ASSURANCE STATEMENT (continued)

Reports to Study Director and Management	01/21/94, 02/03/94, 02/09/94, 03/17/94, 03/25/94, 04/28/94, 07/18/94, 09/08/94, 09/20/94, 03/24/95

This study was conducted in compliance with the Good Laboratory Practice regulations as described by the EPA (40 CFR Part 792) and OECD Annex 2 C(81)30. The reported results accurately reflect the content of the raw data.

Deanna M. Talerico
Senior Quality Assurance Auditor

Date 3-24-95

Raymond V. Karcher, B.A., LAT
Manager of Quality Assurance

Date 3-24-95

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SUMMARY

This study was conducted to provide screening information concerning the potential systemic, reproductive and developmental toxicity of 1-Hexene when administered orally, by gavage, to F0 male and female rats. The study consisted of one control group and three treatment groups with 12 males and 12 females in each group. Three test article components were blended to produce the test article. The blended test article was administered at dosage levels of 100, 500 and 1000 mg/kg/day and a dose volume of 5 mL/kg. The control group received the vehicle, corn oil, at an equivalent dose volume. The F0 males were treated for 28 days prior to mating and until euthanasia (44 days of dosing). The F0 females were treated for 14 days prior to mating, and during mating, gestation, and lactation until euthanasia (41-55 total days of dosing). The animals were observed daily for overt signs of toxicity, and body weights and food consumption were measured at specified intervals. F0 females were allowed to deliver and rear their offspring until lactation day 4. Viability and development of the F1 generation were evaluated. The F0 males and females were euthanized and subjected to a gross necropsy examination. Selected tissues were preserved in Bouin's solution or 10% neutral buffered formalin. The ovaries, testes, epididymides, liver, kidneys, and peripheral (sciatic) nerve of control and high dose animals; the kidneys of low and mid dose animals; and gross lesions from all animals were examined microscopically. Surviving F1 pups were euthanized and necropsied on lactation day 4.

No mortality or clinical signs of toxicity were observed during the study. Similarly, there were no biologically meaningful differences among the groups with respect to mean body weights, weight gain, food consumption or organ weight data. Copulation and fertility indices, precoital intervals, gestation lengths and pregnancy rates were comparable among the groups, and no signs of prolonged delivery or unusual nesting behaviors were noted. F1 pup viability, body weights, external observations and necropsy data were comparable among the groups during lactation days 0 through 4.

Pitted kidneys were observed at necropsy for two males in the 500 mg/kg/day group and three males in the 1000 mg/kg/day group. Test article-related microscopic changes were observed in the kidneys of male rats from the 100, 500 and 1000 mg/kg/day groups. The microscopic findings consisted of accumulations of hyaline droplets in the epithelial cells of the proximal convoluted tubules of the kidneys. The severity of this condition was dose-response related in the treated males. However, this condition, hydrocarbon nephropathy, is specific to young adult male rats and, therefore, is no indication that similar nephropathy will occur in humans exposed to the test article.

In summary, there was no evidence of impaired reproductive capabilities in the F0 generation, or developmental toxicity in the F1 generation. A NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day. Although male-specific nephrotoxicity was observed in treated rats at each level tested in this study, the condition is not considered a potential risk to humans.

I. INTRODUCTION

This report details the experimental procedures and results of an oral reproduction/developmental toxicity screening test in rats with 1-Hexene. This study was sponsored by the Alpha Olefins Panel of the Chemical Manufacturers Association, Washington, DC, and was conducted at Springborn Laboratories, Inc. (SLS), 640 North Elizabeth Street, Spencerville, Ohio. The laboratory rat was selected as the experimental model since it is a preferred species for oral toxicity testing by United States and international regulatory agencies. Oral administration of the test article was selected to assure systemic availability. The GLP initiation date for the study was December 28, 1993. The in-life phase of the main study was initiated on March 14, 1994, and concluded on May 21, 1994.

Prior to the initiation of the main study, a dose range-finding study was conducted in rats to aid in dosage level selection. The experimental procedures and results of the dose range-finding study are presented in Appendix A.

II. OBJECTIVE

The objective of the study was to provide initial screening information concerning the potential systemic, reproductive and developmental toxicity of 1-Hexene when administered orally, by gavage, to F0 male and female rats. The experimental design encompassed gonadal function, estrous cycles, mating, conception and parturition.

III. MATERIALS AND METHODS

A. Experimental Protocol

The study protocol and protocol amendments are presented in Appendix B.

B. Test Article and Control Material

1. Test Article Receipt, Identification and Storage

Three test article components were blended to produce the test article used in this study. Receipt, identification and storage of the test article components are included in the following sections.

a. Test Article Component A

Test article component A, NEODENE 6 alpha olefin, was received at SLS from the Shell Development Company, Houston, Texas, at ambient conditions, and identified as follows:

Assigned SLS ID	Lot (Batch) Number	Physical Description	Receipt Date	Expiration Date
S93.001.3325	20202-45-1049	Clear, colorless liquid	12/02/93	12/94

b. Test Article Component B

Test article component B, Hexene-1 Gulftene 6 , was received at SLS from the Chevron Chemical Company, Baytown, Texas, at ambient conditions, and identified as follows:

Assigned SLS ID	Lot (Batch) Number	Physical Description	Receipt Date	Expiration Date
S94.002.3325	CBN0044	Clear, colorless liquid	01/10/94	None Provided

c. Test Article Component C

Test article component C, Alpha Olefins C6 1-Hexene, was received at SLS from the Ethyl Corporation (now Albemarle™ Corp.), Baton Rouge, Louisiana, at ambient conditions, and identified as follows:

Assigned SLS ID	Lot (Batch) Number	Physical Description	Receipt Date	Expiration Date
S93.003.3325	300-974	Clear, colorless liquid	12/14/93	None Provided

A reserve 1 g sample of each test article component and the blended test article was taken at SLS and stored in amber vials at room temperature, under a nitrogen blanket. Test article component A and the blended test article were stored under a nitrogen blanket from the time of receipt or preparation. Following the method validation preparation, a nitrogen blanket was placed over components B and C. The Sponsor is responsible for any necessary evaluations concerning chemical identification, purity, strength and stability, and will supply the necessary characterization.

2. Control Material (Vehicle) Receipt, Identification and Storage

The vehicle used in the preparation of dosing mixtures and for administration to control animals was Mazola® corn oil. The corn oil was received from Best Foods, Englewood Cliffs, New Jersey, stored at room temperature, and identified as follows:

Lot Numbers	Assigned SLS ID	Receipt Dates	Expiration Dates
APR0695A	V93.045	11/15/93	04/06/95
OCT0494A	V94.007	02/24/94	10/04/94
JUN2695A	V94.012	04/07/94	06/26/95
DEC2194A	V94.013	04/15/94	12/21/94

3. Preparation of the Blended Test Article and Dosing Mixtures

a. Blended Test Article

Equal amounts of test article components A, B and C were weighed into a large beaker. A stir bar was added, the beaker was covered with foil, and the contents of the beaker were stirred for 10 minutes. Two batches of the blended test article were prepared in this manner and then transferred to a 4 liter amber glass container and stirred vigorously for 15 minutes. The blended test article was capped, sealed with teflon tape, placed under a nitrogen blanket and stored at room temperature.

b. Dosing Mixtures

Prior to each preparation, the blended test article was stirred for a minimum of 15 minutes. A specified amount of the blended test article for each dose group was added to a volumetric flask. Approximately one-half of the total corn oil necessary to achieve the desired concentration of the test article was added to each flask, and the flasks were capped and inverted several times. A sufficient quantity of corn oil was then added to each flask to achieve the desired concentration. Each flask was capped and inverted several times. A stir bar was added to each flask, and the contents were stirred for 15 minutes. The dosing mixtures were prepared fresh biweekly, dispensed into daily aliquots and stored refrigerated in clear glass jars. Teflon tape and a nitrogen blanket were utilized for each jar. During each biweekly preparation, a sufficient quantity of corn oil was dispensed into daily aliquots for administration to control animals. Daily aliquots were removed from the refrigerator and equilibrated to room temperature prior to dispensing. Each daily aliquot was stirred for 15 minutes prior to dispensing and then continuously prior to and during dosing.

4. Homogeneity, Stability and Concentration Analyses

Prestudy homogeneity and stability analyses were performed at SLS on concentrations of the blended test article which encompassed those used in this study.

Samples were taken from the top, middle and bottom portions of the blended test article and were analyzed for purity at SLS. Each fresh preparation of the dosing mixtures was analyzed for verification of test article concentration at SLS prior to dose administration. The methodology and results of analyses performed at SLS are presented in Appendix C.

C. Animals and Animal Husbandry

Animal housing and care were based on the standards established by the American Association for Accreditation of Laboratory Animal Care (AAALAC) and the guidelines set forth in the Guide for the Care and Use of Laboratory Animals, NIH Publication No. 86-23, 1985.

1. Animal Receipt, Identification and Housing

Fifty-three male and fifty-three female Sprague-Dawley Crl:CD®BR VAF/Plus® rats were received at SLS from Charles River Laboratories, Inc., Portage, Michigan, on March 3, 1994, and March 17, 1994, respectively, for the main study.

At the time of receipt, each rat was identified with a metal ear tag displaying a unique number. Color coded cage cards displaying the study, animal and group numbers, and the animal's sex were affixed to each cage.

All of the male rats were gang-housed (two or three/cage) for a period of four days following receipt to allow the animals to adjust to the automatic watering system, due to their young age. The males were then housed individually during the remainder of acclimation and while on study (except during cohabitation) in suspended stainless steel cages. The females were housed individually in suspended stainless steel cages during acclimation, prior to cohabitation and during gestation, and then transferred to individual plastic boxes containing nesting material for parturition and lactation.

2. Acclimation

Animals were examined upon receipt and daily thereafter during acclimation for signs of physical or behavioral abnormalities. Only healthy animals were maintained for possible assignment to the study. Mortality checks were performed twice daily, in the morning and afternoon. Individual body weights were determined on the day following receipt and just prior to randomization for assignment to study groups. Animals were acclimated to the laboratory environment for a period of 11 days prior to randomization.

3. Diet and Drinking Water

Pur · · Certified Rodent Chow® #5002 and municipal tap water were provided to each animal ad libitum. The feed was analyzed by the supplier for nutritional components and environmental contaminants. The lot number and expiration date of each batch of feed used during the study were recorded. The tap water was purified by reverse osmosis and supplied to the animals by an automatic watering system (stainless steel caging) or from water bottles (nesting boxes). Water supplying the facility is analyzed on an annual basis for contaminants according to SLS Standard Operating Procedures. The results of the feed and water analyses are maintained at SLS. Within generally acceptable limits, there were no contaminants in the diet or drinking water which would interfere with the conduct of the study.

4. Environmental Conditions

Animals were housed throughout the study in an environment-controlled room with a 12-hour light/12-hour dark cycle and 10 to 12 air changes per hour. The environmental control equipment was monitored and adjusted as necessary to minimize fluctuations in the animal room environment. The desired room temperature and relative humidity were 68 to 74°F and 35 to 65%, respectively. The room temperature and relative humidity ranges were recorded daily.

On forty-three days, the animal room temperature was outside the specified range by +1 to +6°F, and on six days, the relative humidity was outside the specified range by -19 to +6%. These occurrences had no apparent impact on the outcome of the study.

D. Experimental Design and Test Procedures

1. Experimental Design

The following table presents the study group design and dosage levels tested:

Group	No. of Animals Male	Female	Treatment	Dosage Level (mg/kg/day)	Dose Conc. (mg/mL)	Dose Volume (mL/kg)
1	12	12	Vehicle	0	0	5
2	12	12	1-Hexene	100	20	5
3	12	12	1-Hexene	500	100	5
4	12	12	1-Hexene	1000	200	5

2. Test Procedures and Parameters Evaluated

a. F0 Generation

1) Randomization and Group Assignment

At the conclusion of acclimation, animals were weighed and examined. Animals determined to be suitable test subjects, based on age, healthy appearance and body weight, were assigned to groups. A randomization table in a block design was computer-generated based on body weight stratification. At study initiation, the males were six weeks of age with body weights ranging from 195 to 242 g, and the females were eight weeks of age with body weights ranging from 163 to 219 g.

2) Treatment

The dosing preparations were administered orally, by gavage, as a single dose daily. The males were dosed for 28 days prior to mating and until the day prior to euthanasia (44 total days of dosing). The females were dosed for 14 days prior to mating and throughout gestation and lactation, until the day prior to euthanasia (41-55 total days of dosing). Individual doses were calculated based on the most recent body weight data.

3) Clinical Observations

The animals were observed daily for clinical signs of toxicity, including physical and behavioral abnormalities. Mortality checks were performed twice daily, in the morning and afternoon. Post-dose observations were performed daily between one-half hour and two hours following dosing for overt signs of toxicity.

On lactation day 3, post-dose observations for control female #3237 were performed two hours and two minutes following dosing, rather than between one-half hour and two hours following dosing as specified in the protocol. This occurrence had no impact on the outcome of the study.

4) Body Weights

Individual male body weights were measured weekly throughout the study. Individual female body weights were also measured weekly, prior to mating. When positive evidence of mating was detected, body weights were measured on gestation days 0, 7, 14 and 20 and lactation days 1 and 4. One female in group 3 (#3267) was euthanized on post-breeding day 25 and did not have a final body weight taken. This deviation did not have a major impact on the study results.

5) Food Consumption

Individual food consumption for males and females was measured on the same days as the body weights, except during the cohabitation period. Food consumption was not measured while the animals were paired for mating.

6) Breeding

Following 28 days of treatment for the males and 14 days of treatment for the females, each female was cohabitated with a single male from the same treatment group. Each mating pair was observed daily for evidence of copulation. Evidence of mating was determined by the presence of a copulatory plug in the vagina or a sperm positive vaginal smear. The day evidence of copulation was observed was designated day 0 of gestation and the female was returned to individual caging.

If no evidence of copulation was confirmed after ten days of cohabitation, the female was separated from the first male and placed with a second (proven) male from the same treatment group for a maximum of five days. Females with no evidence of mating after a total of fifteen days were separated from their mates and placed in a plastic box containing nesting material.

7) Parturition and Lactation

Females with positive evidence of mating were transferred to individual plastic boxes containing nesting material on gestation day 18. These females were observed for signs of parturition a minimum of twice daily. The time parturition was first detected was recorded, and the females were observed for signs of difficult or prolonged delivery. The day on which parturition was judged complete was designated lactation day 0. The females and their offspring remained together until euthanasia on lactation day 4. The females were observed throughout lactation for abnormal nursing or nesting behaviors. The offspring were designated as the F1 generation.

8) Gross Necropsy

All females were euthanized by carbon dioxide inhalation and subjected to a gross necropsy examination. Females that delivered were necropsied on lactation day 4. Females that failed to deliver were necropsied 25 days after evidence of mating was detected. The thoracic, abdominal and pelvic cavities were opened, and the viscera was examined. The number of uterine implantation scars was recorded for all females, and the ovaries and brain were weighed; paired organs were weighed together. The ovaries, lungs, liver, kidneys, peripheral (sciatic) nerve, and all gross lesions from each female were preserved in 10% neutral buffered formalin for possible future histological examination.

All males were euthanized by carbon dioxide inhalation and subjected to a gross necropsy examination after 43 days of dosing (day 44). The thoracic, abdominal and pelvic cavities were opened, and the viscera were examined. The brain, testes and epididymides were weighed; paired organs were weighed together. The testes, epididymides and accessory sex organs were preserved in Bouin's solution. The liver, kidneys, peripheral (sciatic) nerve, and all gross lesions were preserved in 10% neutral buffered formalin.

The brain of group 2 male #3168 was discarded prior to weight collection. This occurrence had no impact on the outcome of the study or interpretation of study results.

9) Histopathology

The ovaries, testes, epididymides, liver, kidneys, and peripheral (sciatic) nerve of control and high dose animals; the kidneys of the low and mid dose animals; and all gross lesions from each group were processed for microscopic examination. The tissues were trimmed, embedded in paraffin, sectioned and stained with hematoxylin and eosin. Histology was performed by Histo Techniques, 96 Grace Drive, Powell, Ohio. The slides were examined microscopically by Dr. Robert G. Geil, a board-certified veterinary pathologist.

b. F1 Generation

1) Pup Identification

On lactation day 0, the pups in each litter were consecutively identified by toe clipping, beginning with the male offspring.

2) Litter Data

Pup viability was determined on lactation days 0 through 4. A detailed examination of the pups was performed on lactation days 0 and 4. The sex of each pup was determined on lactation day 0 and verified on lactation day 4. Individual pup weights were measured on lactation days 1 and 4.

For additional pups found alive on lactation day 1, toe clipping, detailed examinations, and sex determinations scheduled for lactation day 0 were performed on lactation day 1.

3) Gross Necropsy

All intact pups dying prior to lactation day 4 were necropsied. Emphasis was placed on developmental morphology. Cannibalized or partially cannibalized pups were euthanized by an abdominal cavity injection of sodium pentobarbital, if necessary, and discarded without necropsy. All surviving pups were euthanized by an abdominal cavity injection of sodium pentobarbital and necropsied on lactation day 4. The thoracic, abdominal and pelvic cavities were opened and the viscera examined. All internal gross lesions were preserved in 10% neutral buffered formalin for possible future histopathological examination.

On one day, the method of euthanasia was not documented for the F1 pups. This occurrence had no impact on the outcome of the study.

IV. STATISTICAL ANALYSES

Continuous data, including body weights, body weight gain, food consumption, organ weights, pup body weights, gestation length, mean live litter size and implantation scar counts were analyzed by One-Way Analysis of Variance (ANOVA) [1]. If significance was detected, group by group comparisons were performed using Dunnett's test [2]. Count data were analyzed utilizing Chi-Square test [3] for copulation and fertility indices, pup sex ratios, the number of live and dead pups per group on lactation day 0 and pup survival after lactation day 0. All analyses utilized two-tailed tests for a minimum significance level of 5% comparing the control group to the treated groups.

V. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS

The remaining test article components will be returned to the appropriate supplier, and the blended test article will be properly disposed of at SLS. All original paper data, magnetically encoded records, wet tissues, blocks, slides, and a copy of the final report will be transferred to the SLS archives and stored for a minimum of ten years. The Sponsor will be contacted prior to final disposition of these items.

VI. RESULTS

A. Analytical Chemistry Evaluations

Appendix C (Analytical Chemistry Results)

Prestudy analytical chemistry evaluations indicated that the blended test article was homogeneous and stable in corn oil for up to 15 days when stored refrigerated. The average purity of the blended test article was 98.9%. Analysis of dosing mixtures resulted in average test article recoveries ranging from 92.2 to 108.3%, indicating that the mixtures were accurately prepared.

B. F0 Generation

1. Survival and Clinical Observations

Tables 1 and 2 (Summary Data)
Appendices D and E (Individual Data)

All males survived to scheduled euthanasia on study day 44. One female in the 500 mg/kg/day group failed to deliver and was euthanized 25 days after evidence of mating was detected. The female was found to be gravid, and contained one autolyzed pup. All other females survived to study termination on lactation day 4.

No overt clinical signs of toxicity were noted in males or females from any of the study groups. Incidental findings were observed sporadically throughout the control and treated groups, and included dark material around the nose, scabbing, and hairloss (primarily on the forelimbs).

2. Body Weights and Weight Gain

Tables 3-10 (Summary Data)
Appendices F-M (Individual Data)

There were no statistically significant or biologically meaningful differences noted in mean body weights or body weight gains. Mean weights and weight gains for males and females were comparable among the groups throughout the study.

3. Food Consumption

Tables 11-18 (Summary Data)
Appendices N-U (Individual Data)

Male food consumption, calculated as grams/animal/day and grams/kg/day, was similar among the groups throughout the study; no statistical differences were noted.

Food consumption calculated as grams/kg/day was statistically increased for females in the 100, 500 and 1000 mg/kg/day groups during gestation days 7-14, and for females in the 500 mg/kg/day group during gestation days 14-20. These increases were not considered meaningful since similar statistical differences were not observed in grams/animal/day food consumption during these intervals. There were no statistical differences in female food consumption (grams/animal/day or grams/kg/day) prior to mating or during lactation.

4. Fertility, Gestation, Parturition and Lactation

Tables 19 and 20 (Summary Data)
Appendices V and W (Individual Data)
Appendix JJ (SLS Historical Control Data)

Male and female copulation and fertility indices (i.e. pregnancy vs. successful copulation), precoital intervals, and gestation lengths were comparable among the groups; and the pregnancy rate was 100% in each group. There were no signs of prolonged delivery or unusual nesting behaviors noted in any of the study groups. However, one female in the 500 mg/kg/day group was euthanized on post-coital day 25 and was found to contain one autolyzed pup.

5. Gross Necropsy Observations

Tables 21 and 22 (Summary Data)
Appendices X and Y (Individual Data)
Appendix II (Implantation Loss)

Pitted kidneys were observed at necropsy for 2 of 12 males in the 500 mg/kg/day group, and 3 of 12 males in the 1000 mg/kg/day group. The pitted kidneys were possibly related to the hydrocarbon nephropathy observed microscopically in the male rats. Other gross necropsy findings for males were generally unremarkable.

Gross necropsy findings for females that delivered were generally unremarkable, and the mean implantation scar counts for these females were comparable among the groups.

For one 500 mg/kg/day female euthanized post-breeding day 25 (#3267), gross necropsy findings included dark red mucoid contents in the uterus, with one elongated and partially autolyzed pup located in the left uterine horn extending into the left cervix.

6. Organ Weights

Tables 23-26 (Summary Data)
Appendices Z-CC (Individual Data)

Absolute epididymide weights for males in the 100, 500 and 1000 mg/kg/day groups were slightly, but statistically lower than the control group. Epididymide weights relative to brain weights were also slightly lower than controls for males in each treated group, however, the difference was only statistically significant at the 100 mg/kg/day level. Absolute and relative testes weights were comparable between the groups.

Absolute ovary weights and ovary weights relative to brain weight were comparable between the groups.

7. Histopathology

Appendix DD (Histopathology Report)

Test article-related microscopic changes were limited to the kidneys of male rats from the 100, 500 and 1000 mg/kg/day groups. Most male rats in these groups had accumulations of hyaline droplets in the epithelial cells of the proximal convoluted tubules of the kidneys. There was a positive dose-response relationship in the severity of this condition in the three treated groups. However, this condition is specific to young adult male rats and is of questionable toxicological significance [4, 5, 6].

Other microscopic lesions in the organs and tissues examined were considered spontaneous and not related to treatment with the test article.

C. F1 Generation

1. Pup Viability

Table 27 (Summary Data)
Appendix EE (Individual Data)
Appendix JJ (SLS Historical Control Data)

The number of live and dead pups, the number of litters with live offspring, the mean live litter size and the male to female pup ratio were comparable among the groups on lactation day 0. Pup survival was comparable among the groups on lactation days 1 and 4.

2. External Observations

Table 28 (Summary Data)
Appendix FF (Individual Data)

There were no unusual external observations noted in the pups during lactation days 0 to 4. Incidental findings commonly observed in young offspring occurred in each group, including controls.

3. Body Weights

Table 29 (Summary Data)
Appendix GG (Individual Data)
Appendix JJ (SLS Historical Control Data)

Mean pup weights were comparable among the groups on lactation days 0 and 4.

4. Necropsy Observations

Table 30 (Summary Data)
Appendix HH (Individual Data)

No remarkable findings were observed at necropsy in pups found dead prior to lactation day 4, or pups euthanized at study termination on lactation day 4. Incidental findings common to developing rat offspring were noted in each group, including controls.

VII. DISCUSSION

The potential systemic, reproductive and developmental toxicity of 1-Hexene was evaluated in this screening study in rats.

No mortality or clinical signs of toxicity were observed during the study. Similarly, there were no biologically meaningful differences among the groups with respect to mean body weights, weight gain or food consumption.

Male and female copulation and fertility indices, precoital intervals, gestation lengths and pregnancy rates were comparable among the groups, and there were no signs of prolonged delivery or unusual nesting behaviors noted in any of the study groups.

Pitted kidneys were observed at necropsy for 2 of 12 males in the 500 mg/kg/day group and 3 of 12 males in the 1000 mg/kg/day group. All other necropsy findings were generally unremarkable for both males and females. Absolute and relative epididymide

weights for males in the 100, 500 and 1000 mg/kg/day groups were decreased when compared to the control group. However, since no apparent test article-related changes were observed in the epididymides during microscopic examinations, there was no evidence of impaired fertility in the treated males and there was a lack of dose response between the groups, the decreased weights were not considered to be toxicologically significant.

Test article-related microscopic changes were observed in the kidneys of male rats from the 100, 500 and 1000 mg/kg/day groups. Most male rats in these groups had accumulations of hyaline droplets in the epithelial cells of the proximal convoluted tubules of the kidneys, and there was a positive dose-response relationship in the severity of this condition in the three treated groups. However, this condition, hydrocarbon nephropathy, is specific to young adult male rats and, therefore, is of questionable toxicological significance. Since hyaline droplets are not found in humans, the male-specific nephrotoxicity observed in this study is no indication that induction of similar nephropathy will occur in humans exposed to the test article [4, 5, 6].

F1 pup viability, body weights, external observations and necropsy data were comparable among the groups during lactation days 0 through 4.

VIII. CONCLUSION

Oral administration of 1-Hexene to F0 parental animals produced dose-related hydrocarbon nephropathy in male rats at dosage levels of 100, 500 and 1000 mg/kg/day. However, since the nephropathy is specific to young adult male rats, this condition is not considered a potential risk to humans. There was no evidence of impaired reproductive capabilities in the F0 generation, or developmental toxicity in the F1 generation through lactation day 4. The NOAEL for reproductive toxicity is 1000 mg/kg/day.

Elaine M Daniel

Elaine M. Daniel, Ph.D., DABT
Study Director

Date 3/24/95

IX. REPORT REVIEW

Kok-Wah Hew, Ph.D.
Manager of Reproductive Toxicology

Date 3/24/95

Dean E. Rodwell, M.S.
Director of Reproductive Toxicology

Date 3/24/95

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TABLE 1

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F0 MALE SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

----- M A L E -----

GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
NORMAL				
-NO CLINICAL SIGNS	445/ 12	491/ 12	457/ 12	439/ 12
DEAD				
-SCHEDULED EUTHANASIA	12/ 12	12/ 12	12/ 12	12/ 12
BODY				
-OPEN LESIONS - VENTRAL NECK	10/ 1	0/ 0	0/ 0	0/ 0
-SCAB(S) - RIGHT LATERAL HEAD	0/ 0	3/ 1	0/ 0	0/ 0
-SCAB(S) - VENTRAL NECK	31/ 1	0/ 0	0/ 0	0/ 0
-SCAB(S) - RIGHT SHOULDER	18/ 1	0/ 0	0/ 0	0/ 0
-SCAB(S) - LEFT SHOULDER	0/ 0	0/ 0	0/ 0	2/ 1
-SCAB(S) - LEFT FORELIMB	0/ 0	1/ 1	1/ 1	10/ 1
-APPARENT UMBILICAL HERNIA	0/ 0	2/ 1	0/ 0	0/ 0
-REDDISH STAINING - UROGENITAL AREA	4/ 2	0/ 0	0/ 0	3/ 2
-URINE STAIN - UROGENITAL AREA	1/ 1	0/ 0	0/ 0	0/ 0
HAIRLOSS				
-LEFT FORELIMB	6/ 1	14/ 2	26/ 1	54/ 2
-RIGHT FORELIMB	1/ 1	14/ 2	25/ 1	39/ 2
-LEFT HINDLIMB	0/ 0	0/ 0	3/ 1	21/ 1
-RIGHT HINDLIMB	0/ 0	0/ 0	0/ 0	18/ 1
-LEFT LATERAL ABDOMINAL	0/ 0	0/ 0	2/ 1	0/ 0
-ABDOMINAL REGION	0/ 0	0/ 0	17/ 1	0/ 0
-VENTRAL NECK	25/ 1	0/ 0	0/ 0	0/ 0
EYES				
-DARK MATERIAL AROUND EYE(S)	5/ 1	0/ 0	1/ 1	0/ 0
NOSE/MOUTH				
-DARK MATERIAL AROUND NOSE	16/ 4	6/ 1	27/ 8	29/ 4
-MALALIGNMENT - UPPER INCISOR(S)	7/ 1	11/ 1	1/ 1	0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 1

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F0 MALE SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

----- M A L E -----

GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
OTHER				
-AN UNDETERMINED AMOUNT OF APPARENT TEST ARTICLE CAME FROM ANIMAL'S MOUTH DURING DOSE ADMINISTRATION	0/ 0	0/ 0	1/ 1	1/ 1
POST-DOSE OBSERVATIONS				
-DARK MATERIAL AROUND EYE(S)	0/ 0	0/ 0	0/ 0	1/ 1
-DARK MATERIAL AROUND NOSE	0/ 0	0/ 0	0/ 0	2/ 1
-DARK MATERIAL AROUND MOUTH	0/ 0	0/ 0	0/ 0	1/ 1
-RALES	0/ 0	0/ 0	0/ 0	1/ 1

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 2

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF FO FEMALE SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

----- F E M A L E -----

GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
NORMAL				
-NO CLINICAL SIGNS	494/ 12	496/ 12	472/ 12	488/ 12
DEAD				
-EUTHANIZED - POST-BREEDING DAY 25	0/ 0	0/ 0	1/ 1	0/ 0
-SCHEDULED EUTHANASIA	12/ 12	12/ 12	11/ 11	12/ 12
EXCRETA/EMESIS				
-FEW FECES	1/ 1	0/ 0	0/ 0	0/ 0
-RED VAGINAL DISCHARGE	0/ 0	1/ 1	2/ 2	1/ 1
BODY				
-SCAB(S) - LEFT FORELIMB	0/ 0	3/ 1	0/ 0	10/ 2
-SCAB(S) - RIGHT FORELIMB	3/ 1	6/ 1	0/ 0	10/ 2
HAIRLOSS				
-VENTRAL NECK	0/ 0	0/ 0	0/ 0	14/ 1
-LEFT FORELIMB	55/ 2	14/ 2	35/ 3	24/ 3
-RIGHT FORELIMB	61/ 3	19/ 3	49/ 3	25/ 3
-RIGHT HINDLIMB	0/ 0	6/ 1	0/ 0	0/ 0
-VENTRAL THORACIC	0/ 0	0/ 0	0/ 0	14/ 1
-ABDOMINAL REGION	0/ 0	0/ 0	0/ 0	14/ 1
-RIGHT INGUINAL	0/ 0	0/ 0	0/ 0	1/ 1
-UROGENITAL AREA	0/ 0	0/ 0	0/ 0	9/ 1
NOSE/MOUTH				
-UPPER INCISOR(S) - BROKEN	0/ 0	0/ 0	0/ 0	4/ 1
-DARK MATERIAL AROUND NOSE	0/ 0	0/ 0	2/ 1	4/ 1
-SCAB(S) - RIGHT CORNER OF MOUTH	6/ 1	0/ 0	0/ 0	0/ 0
OTHER				
-AN UNDETERMINED AMOUNT OF APPARENT TEST ARTICLE CAME FROM ANIMAL'S MOUTH DURING DOSE ADMINISTRATION	0/ 0	0/ 0	0/ 0	2/ 2

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 2

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CHA SUMMARY OF F0 FEMALE SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

----- F E M A L E -----

GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
POST-DOSE OBSERVATIONS				
-DARK MATERIAL AROUND THE NOSE	0/ 0	0/ 0	0/ 0	1/ 1

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 3

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 1

CLIENT: CMA SUMMARY OF FO MALE BODY WEIGHT DATA (GRAMS)

----- M A L E -----

	GROUP: LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 1					
	MEAN	219	218	218	218
	S.D.	12.5	12.9	12.6	13.1
	N	12	12	12	12
2					
	MEAN	281	282	280	283
	S.D.	20.5	16.8	15.7	20.0
	N	12	12	12	12
3					
	MEAN	341	340	337	342
	S.D.	23.7	21.6	18.0	25.5
	N	12	12	12	12
4					
	MEAN	399	393	389	395
	S.D.	27.4	27.1	21.1	30.4
	N	12	12	12	12
5					
	MEAN	445	437	428	435
	S.D.	31.3	32.6	23.4	32.9
	N	12	12	12	12
6					
	MEAN	476	468	454	461
	S.D.	29.4	37.6	25.6	37.4
	N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 3

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CHA SUMMARY OF F0 MALE BODY WEIGHT DATA (GRAMS)

----- M A L E -----

GROUP: / LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 7				
MEAN	513	502	485	493
S.D.	34.2	40.2	29.9	43.7
N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 4

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CHA SUMMARY OF F0 MALE BODY WEIGHT GAIN DATA (GRAMS)

----- M A L E -----

GROUP: / LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 1 TO 2				
MEAN	62	64	62	65
S.D.	9.6	5.3	6.2	8.3
N	12	12	12	12
2 TO 3				
MEAN	61	58	57	59
S.D.	7.0	7.2	6.9	7.8
N	12	12	12	12
3 TO 4				
MEAN	58	53	51	53
S.D.	8.1	8.6	9.3	6.8
N	12	12	12	12
4 TO 5				
MEAN	46	44	39	40
S.D.	8.8	6.9	7.5	8.3
N	12	12	12	12
5 TO 6				
MEAN	32	31	26	26
S.D.	7.4	7.3	8.2	7.9
N	12	12	12	12
6 TO 7				
MEAN	37	34	31	32
S.D.	7.8	6.2	5.9	7.9
N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 5

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F0 FEMALE BODY WEIGHT DATA PRIOR TO MATING (GRAMS)

----- F E M A L E -----

	GROUP: LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 1					
	MEAN	191	191	191	191
	S.D.	13.9	14.9	15.3	13.7
	N	12	12	12	12
2					
	MEAN	206	207	204	206
	S.D.	16.0	15.4	14.9	15.5
	N	12	12	12	12
3					
	MEAN	219	220	213	217
	S.D.	18.1	16.5	12.8	17.4
	N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 6

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F0 FEMALE BODY WEIGHT GAIN DATA PRIOR TO MATING (GRAMS)

----- F E M A L E -----

GROUP: / LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 1 TO 2				
MEAN	15	16	14	15
S.D.	6.7	4.5	6.9	6.6
N	12	12	12	12
2 TO 3				
MEAN	14	13	8	11
S.D.	6.1	3.0	5.3	8.5
N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 7

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F0 GESTATION BODY WEIGHT DATA (GRAMS)

	GROUP: LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
DAY 0	MEAN	230	225	222	222
	S.D.	26.3	14.7	17.5	17.1
	N	12	12	12	12
DAY 7	MEAN	264	263	252	261
	S.D.	22.5	20.0	16.4	17.3
	N	12	12	12	12
DAY 14	MEAN	297	299	286	297
	S.D.	26.5	21.9	19.6	20.0
	N	12	12	12	12
DAY 20	MEAN	370	376	361	369
	S.D.	28.5	26.8	36.6	28.8
	N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 8

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F0 GESTATION BODY WEIGHT GAIN DATA (GRAMS)

	GROUP:	1	2	3	4
	LEVEL:	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 0- 7	MEAN	35	38	31	39
	S.D.	7.6	7.8	5.2	7.0
	N	12	12	12	12
DAY 7- 14	MEAN	33	37	34	36
	S.D.	8.5	6.2	6.8	6.8
	N	12	12	12	12
DAY 14- 20	MEAN	72	76	75	72
	S.D.	12.6	8.5	19.4	16.1
	N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 9

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F0 LACTATION BODY WEIGHT DATA (GRAMS)

	GROUP:	1	2	3	4
	LEVEL:	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 1	MEAN	283	283	275	280
	S.D.	24.2	27.5	14.2	25.1
	N	12	12	11	12
DAY 4	MEAN	301	301	298	294
	S.D.	21.7	21.5	14.2	24.7
	N	12	12	11	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 10

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F0 LACTATION BODY WEIGHT GAIN DATA (GRAMS)

	GROUP:	1	2	3	4
	LEVEL:	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 1- 4	MEAN	18	18	23	14
	S.D.	5.7	9.1	10.7	8.6
	N	12	12	11	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 11

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 1
CLIENT: CMA SUMMARY OF FO MALE FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

----- M A L E -----

GROUP: LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 1 TO 2				
MEAN	26	26	26	26
S.D.	2.4	1.5	2.3	2.6
N	12	12	12	12
2 TO 3				
MEAN	27	27	27	27
S.D.	2.9	1.6	2.1	2.1
N	12	12	12	12
3 TO 4				
MEAN	27	26	27	27
S.D.	2.7	2.1	2.2	2.2
N	12	12	12	12
4 TO 5				
MEAN	28	27	27	28
S.D.	3.5	2.2	2.1	2.8
N	12	12	12	12
6 TO 7				
MEAN	28	27	26	27
S.D.	3.4	3.0	2.5	2.8
N	6	12	12	10

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL
NOTE: FOOD CONSUMPTION WAS NOT MEASURED FOR MALES MATING DURING WEEKS 5-6 AND 6-7.

TABLE 12

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F0 MALE FOOD CONSUMPTION DATA (GRAMS/KG/DAY)

----- M A L E -----

	GROUP: LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 1 TO 2					
	MEAN	105	106	106	105
	S.D.	5.4	4.2	7.4	6.6
	N	12	12	12	12
2 TO 3					
	MEAN	87	85	89	87
	S.D.	6.1	3.4	6.7	2.8
	N	12	12	12	12
3 TO 4					
	MEAN	74	71	74	72
	S.D.	5.1	3.0	6.6	3.5
	N	12	12	12	12
4 TO 5					
	MEAN	67	66	67	67
	S.D.	5.9	2.3	5.4	5.3
	N	12	12	12	12
6 TO 7					
	MEAN	56	55	55	56
	S.D.	4.8	3.5	4.7	3.3
	N	6	12	12	10

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

NOTE: FOOD CONSUMPTION WAS NOT MEASURED FOR MALES MATING DURING WEEKS 5-6 AND 6-7.

TABLE 13

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F0 FEMALE FOOD CONSUMPTION DATA PRIOR TO MATING (GRAMS/ANIMAL/DAY)

----- F E M A L E -----

GROUP: / LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 1 TO 2				
MEAN	15	16	15	15
S.D.	1.2	1.6	0.9	1.6
N	12	12	12	12
2 TO 3				
MEAN	15	16	15	15
S.D.	1.2	2.3	1.0	1.5
N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 14

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF FO FEMALE FOOD CONSUMPTION DATA PRIOR TO MATING (GRAMS/KG/DAY)

----- F E M A L E -----

GROUP: / LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
WEEK 1 TO 2				
MEAN	74	78	75	76
S.D.	4.5	6.3	4.2	6.4
N	12	12	12	12
2 TO 3				
MEAN	71	76	72	73
S.D.	3.7	9.8	5.5	4.9
N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 15

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 1

CLIENT: CMA SUMMARY OF F0 GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

	GROUP:	1	2	3	4
	LEVEL:	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 0- 7	MEAN	19	20	18	19
	S.D.	1.2	2.7	1.4	2.2
	N	12	12	12	12
DAY 7- 14	MEAN	20	22	21	22
	S.D.	2.8	2.6	1.8	2.4
	N	12	12	12	12
DAY 14- 20	MEAN	22	23	23	23
	S.D.	1.4	2.8	1.7	2.3
	N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 16

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F0 GESTATION FOOD CONSUMPTION DATA (GRAMS/KG/DAY)

	GROUP: LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
DAY 0- 7	MEAN	76	81	77	80
	S.D.	8.1	8.2	7.7	7.8
	N	12	12	12	12
DAY 7- 14	MEAN	70	78*	79*	77*
	S.D.	9.3	6.1	5.0	6.4
	N	12	12	12	12
DAY 14- 20	MEAN	65	67	72**	68
	S.D.	5.9	5.8	5.3	4.4
	N	12	12	12	12

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P <0.05; ** = P <0.01

TABLE 17

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 1
CLIENT: CMA SUMMARY OF F0 LACTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

	GROUP:	1	2	3	4
	LEVEL:	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 1- 4	MEAN	32	30	31	34
	S.D.	2.7	4.9	6.8	14.9
	N	12	12	11	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 18

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF FO LACTATION FOOD CONSUMPTION DATA (GRAMS/KG/DAY)

	GROUP:	1	2	3	4
	LEVEL:	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 1- 4	MEAN	111	103	107	117
	S.D.	13.4	16.4	23.8	48.8
	N	12	12	11	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 19

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF FO COPULATION, FERTILITY AND GESTATION LENGTH DATA

GROUP/ LEVEL	COPULATION INDEX (%) FEMALES NO.	%	MALES NO.	%	FERTILITY INDEX (%) FEMALES NO.	%	MALES NO.	%		PRECOITAL INTERVAL (DAYS)		GESTATION LENGTH (DAYS)
1									MEAN	3.8	MEAN	21.9
0 MG/KG/DAY	12/12	100.0	10/12	83.3	12/12	100.0	10/10	100.0	S.D.	2.7	S.D.	0.3
									N	12	N	12
2									MEAN	2.4	MEAN	21.6
100 MG/KG/DAY	12/12	100.0	12/12	100.0	12/12	100.0	12/12	100.0	S.D.	0.9	S.D.	0.5
									N	12	N	12
3									MEAN	2.9	MEAN	21.9
500 MG/KG/DAY	12/12	100.0	12/12	100.0	12/12	100.0	12/12	100.0	S.D.	1.2	S.D.	0.3
									N	12	N	11
4									MEAN	2.8	MEAN	21.8
1000 MG/KG/DAY	12/12	100.0	11/12	91.7	12/12	100.0	11/11	100.0	S.D.	1.7	S.D.	0.4
									N	12	N	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

NOTE: COPULATION INDEX = NO. OF ANIMALS WITH SUCCESSFUL COPULATION / NO. OF MATED ANIMALS X 100.
FEMALE FERTILITY INDEX = NO. OF PREGNANT FEMALES / NO. OF FEMALES WITH SUCCESSFUL COPULATION X 100.
MALE FERTILITY INDEX = NO. OF GRAVID ANIMALS (INITIAL MATING ONLY) / NO. OF MALES WITH SUCCESSFUL COPULATION X 100.

TABLE 20

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 1
CLIENT: CMA SUMMARY OF F0 PREGNANCY STATUS

GROUP:	1		2		3		4	
LEVEL:	0 MG/KG/DAY		100 MG/KG/DAY		500 MG/KG/DAY		1000 MG/KG/DAY	
	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	12		12		12		12	
FEMALES THAT DELIVERED	12	--	12	--	11	--	12	--
FEMALES THAT DID NOT DELIVER	0	--	0	--	1	--	0	--
NONGRAVID AT NECROPSY	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID AT NECROPSY	0	0.0	0	0.0	1	100.0	0	0.0
TOTAL NUMBER OF GRAVID FEMALES	12	100.0	12	100.0	12	100.0	12	100.0

TABLE 21

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F0 MALE GROSS NECROPSY OBSERVATIONS

SCHEDULED EUTHANASIA

	MALE			
GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	12
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA	12	12	12	12
NO REMARKABLE FINDINGS	9	10	7	5
EXTERNAL APPEARANCE				
-INCISOR(S) - MALALIGNED	1	0	1	0
-SKIN - SCABBING	1	0	1	0
-HAIRLOSS	2	2	1	2
-HAIRCOAT - DRIED RED MATTED MATERIAL	0	0	1	0
-HAIRCOAT - DRIED DARK RED MATTED MATERIAL	1	0	0	1
KIDNEYS				
-PITTED	0	0	2	3
SEMINAL VESICLE				
-ADHESION	0	0	0	1
-AGENESIS	0	0	0	1
SPLEEN				
-TAN AREA(S)	0	0	0	1
-ENLARGED	0	0	0	1
THYMUS GLAND				
-REDDENED	0	0	0	1

TABLE 22

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F0 FEMALE GROSS NECROPSY OBSERVATIONS

FEMALES THAT DELIVERED

		FEMALE			
GROUP:		1	2	3	4
LEVEL (MG/KG/DAY):		0	100	500	1000
NUMBER OF ANIMALS IN DOSE GROUP		12	12	12	12
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA		12	12	11	12
EXTERNAL APPEARANCE					
-HAIRLOSS		2	3	2	4
-SKIN - SCABBING		0	1	0	2
KIDNEYS					
-DILATED PELVIS		0	1	0	0
LIVER					
-WHITISH-TAN FOCI		0	0	1	0
MEDIASTINAL LYMPH NODE					
-REDDENED		0	0	0	1
THYMUS GLAND					
-REDDENED		1	0	0	0
URETERS					
-CALCULI		0	1	0	0
-DISTENDED		0	1	0	0
URINARY BLADDER					
-THICKENED		0	1	0	0
UTERUS					
-IMPLANTATION SCAR(S) PRESENT	MEAN	15.7	15.3	15.4	14.4
	S.D.	1.9	1.6	1.2	2.9

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 22

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F0 FEMALE GROSS NECROPSY OBSERVATIONS

FEMALE EUTHANIZED POST-BREEDING DAY 25

	----- FEMALE -----			
GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
NUMBER OF ANIMALS IN DOSE GROUP	12	12	12	12
NUMBER OF ANIMALS EXAMINED POST-BREEDING DAY 25	0	0	1	0
UTERUS				
-DARK RED MUCOID CONTENTS	0	0	1	0
-RETAINED PUP	0	0	1	0
-IMPLANTATION SCAR(S) PRESENT	0	0	1	0

NOTE: THIS FEMALE FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER EVIDENCE OF MATING WAS DETECTED.

TABLE 23

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 1
CLIENT: CMA SUMMARY OF F0 MALE ABSOLUTE ORGAN WEIGHT DATA (GRAMS) WEEK 7

----- M A L E -----

GROUP: / LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
BRAIN				
MEAN	2.27	2.20	2.24	2.20
S.D.	0.075	0.084	0.120	0.108
N	12	11	12	12
EPIDIDYMIDES				
MEAN	1.36	1.22**	1.26*	1.24**
S.D.	0.110	0.094	0.083	0.078
N	12	12	12	12
TESTES				
MEAN	3.87	3.72	3.72	3.82
S.D.	0.321	0.276	0.224	0.272
N	12	12	12	12

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01

TABLE 24

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 1
CLIENT: CMA SUMMARY OF FO MALE ORGAN WEIGHT TO BRAIN WEIGHT DATA (GRAMS/100 GRAMS) WEEK 7

----- M A L E -----

GROUP: / LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
EPIDIDYMIDES				
MEAN	60.048	54.943*	56.268	56.266
S.D.	4.3247	4.4553	3.9084	3.4050
N	12	11	12	12
TESTES				
MEAN	170.857	167.490	166.094	173.285
S.D.	11.2466	12.0049	12.7963	9.3446
N	12	11	12	12

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05

TABLE 25

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 1
CLIENT: CMA SUMMARY OF F0 FEMALE ABSOLUTE ORGAN WEIGHT DATA (GRAMS) WEEK 7

----- F E M A L E -----

GROUP: LEVEL:	1 0 MG/KG/DAY	2 100 MG/KG/DAY	3 500 MG/KG/DAY	4 1000 MG/KG/DAY
BRAIN				
MEAN	2.07	2.09	2.06[a]	2.09
S.D.	0.070	0.074	0.090	0.066
N	12	12	12	12
OVARIES				
MEAN	0.1284	0.1248	0.1272[a]	0.1238
S.D.	0.02533	0.02960	0.02795	0.02569
N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL
[a]INCLUDES ONE FEMALE THAT WAS EUTHANIZED POST-BREEDING DAY 25.

TABLE 26

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F0 FEMALE ORGAN WEIGHT TO BRAIN WEIGHT DATA (GRAMS/100 GRAMS)

----- F E M A L E -----

GROUP:	1	2	3	4
LEVEL:	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
OVARIES				
MEAN	6.184	5.946	6.141[a]	5.944
S.D.	1.1222	1.2693	1.1638	1.2923
N	12	12	12	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL
[a]INCLUDES ONE FEMALE THAT WAS EUTHANIZED POST-BREEDING DAY 25.

TABLE 27

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F1 PUP VIABILITY

LACTATION DAY 0

GROUP	LEVEL	NO. DEAD	NO. LIVE	NO. LITTERS WITH LIVE OFFSPRING	MEAN LIVE LITTER SIZE	SEX RATIO M:F
1	0 MG/KG/DAY	1	174	12	14.5	84: 90
2	100 MG/KG/DAY	4	172	12	14.3	86: 86
3	500 MG/KG/DAY	2	156	11	14.2	78: 78
4	1000 MG/KG/DAY	2	165	12	13.8	91: 74

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL
NOTE: NO. DEAD = TOTAL PUPS STILLBORN, MISSING AND/OR CANNIBALIZED.

TABLE 27

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F1 PUP VIABILITY

DURING LACTATION

GROUP	LEVEL	DAY 1 NO. ALIVE/PUPS	DAY 1 NO. %	DAY 4 NO. ALIVE/PUPS	DAY 4 NO. %
1	0 MG/KG/DAY	172/174	98.9	170/174	97.7
2	100 MG/KG/DAY	170/172	98.8	170/172	98.8
3	500 MG/KG/DAY	154/156	98.7	153/156	98.1
4	1000 MG/KG/DAY	165/165	100.0	165/165	100.0

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 28

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CMA SUMMARY OF F1 PUP OBSERVATIONS DURING LACTATION (OCCURRENCE/ANIMALS AFFECTED)

GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
NORMAL				
-NO REMARKABLE OBSERVATIONS	339/172	310/169	297/155	306/163
DEAD				
-FOUND DEAD	1/ 1	3/ 3	5/ 5	2/ 2
-CANNIBALIZED	0/ 0	1/ 1	0/ 0	0/ 0
-MISSING - PRESUMED CANNIBALIZED	4/ 4	2/ 2	0/ 0	0/ 0
BODY				
-LACERATION(S)	0/ 0	0/ 0	0/ 0	4/ 4
-PUP COOL TO THE TOUCH	2/ 2	0/ 0	0/ 0	0/ 0
-PUP PALE IN COLOR	2/ 2	1/ 1	0/ 0	0/ 0
-SCAB(S)	2/ 2	7/ 7	7/ 7	12/ 12
-SUBCUTANEOUS HEMORRHAGE(S)	1/ 1	16/ 16	5/ 5	12/ 12
ACTIVITY				
-GASPING	1/ 1	0/ 0	0/ 0	0/ 0
OTHER				
-PUP SMALL IN SIZE	1/ 1	8/ 8	0/ 0	0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH CLINICAL FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 29

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE

CLIENT: CHA SUMMARY OF F1 PUP WEIGHTS DURING LACTATION (GRAMS)

	GROUP:	1	2	3	4
	LEVEL:	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 1	MEAN	6.7	6.3	6.6	6.6
	S.D.	0.41	0.53	0.46	0.46
	N	12	12	11	12
DAY 4	MEAN	9.5	8.9	9.3	9.3
	S.D.	0.89	0.88	0.90	0.91
	N	12	12	11	12

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 30

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE
CLIENT: CMA SUMMARY OF F1 PUP GROSS NECROPSY OBSERVATIONS

PUPS FOUND DEAD DURING LACTATION

	PUPS / LITTER			
GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
NUMBER EXAMINED VISCERALLY	1/ 1	3/ 3	4/ 3	2/ 2
NO REMARKABLE FINDINGS	0/ 0	0/ 0	2/ 2	0/ 0
STOMACH				
MILK PRESENT	0/ 0	0/ 0	0/ 0	0/ 0
MILK ABSENT	1/ 1	3/ 3	3/ 3	2/ 2
FINDINGS				
ABDOMINAL CAVITY - DIAPHRAGM, LIVER, STOMACH, INTESTINES, SPLEEN AND URINARY/REPRODUCTIVE TRACT TOO AUTOLYZED TO EXAMINE	0/ 0	0/ 0	1/ 1	0/ 0
LUNG(S) - ATELECTASIS	0/ 0	3/ 3	1/ 1	2/ 2
URETER(S) - DISTENDED	0/ 0	0/ 0	1/ 1	1/ 1
SPINAL COLUMN - VERTEBRAL AGENESIS	0/ 0	1/ 1	0/ 0	0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH NECROPSY FINDING OVER THE NUMBER OF LITTERS EXHIBITING THE FINDING.

TABLE 30

SLS STUDY NO.: 3325.1 REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN RATS WITH 1-HEXENE PAGE 2
CLIENT: CMA SUMMARY OF F1 PUP GROSS NECROPSY OBSERVATIONS

SCHEDULED EUTHANASIA

	PUPS / LITTER			
GROUP:	1	2	3	4
LEVEL (MG/KG/DAY):	0	100	500	1000
NUMBER EXAMINED VISCERALLY	170/12	170/12	153/11	165/12
NO REMARKABLE FINDINGS	145/12	136/12	131/11	137/12
FINDINGS				
EXTERNAL APPEARANCE - SCABBING	2/ 2	8/ 5	7/ 5	11/ 5
EXTERNAL APPEARANCE - OPEN LESIONS	0/ 0	0/ 0	0/ 0	1/ 1
EXTERNAL APPEARANCE - SUBCUTANEOUS HEMORRHAGE	0/ 0	1/ 1	0/ 0	2/ 2
EYES - GLOBE APPEARS HEMORRHAGIC	0/ 0	1/ 1	0/ 0	0/ 0
EYES - HEMORRHAGIC RING AROUND IRIS	0/ 0	0/ 0	0/ 0	1/ 1
EYES - MICROPHTHALMIA	0/ 0	0/ 0	0/ 0	1/ 1
LIVER - PALE	0/ 0	0/ 0	0/ 0	3/ 1
URETER(S) - DISTENDED	23/ 6	25/ 8	16/ 4	12/ 5

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH NECROPSY FINDING OVER THE NUMBER OF LITTERS EXHIBITING THE FINDING.